

# Disordered pigmentation, spastic paraparesis and peripheral neuropathy in three siblings: a new neurocutaneous syndrome

A ABDALLAT, S M DAVIS, J FARRAGE, AND W I McDONALD

*From the King Hussein Medical Centre, Amman, Jordan and the National Hospitals, Queen Square and Maida Vale, London.*

**SUMMARY** Three siblings in a Jordanian family presented with a distinctive syndrome consisting of disordered skin and hair pigmentation, progressive spastic paraparesis and peripheral neuropathy. Sural nerve biopsy revealed axonal degeneration and skin biopsy showed abnormal epidermal pigmentation. Skin fibroblast repair studies were normal. No underlying biochemical defect has been found in this previously undescribed neurocutaneous syndrome.

Many syndromes in which disorders of the skin are associated with abnormalities of the nervous system have been described.<sup>1,2</sup> We have seen recently a family in which several members showed a distinctive association of abnormal skin and hair pigmentation and progressive gait disorder which seems not to have been described previously.

## Case report

### *Case 1*

A 21-year-old Jordanian civil servant was referred for investigation of abnormal skin and hair pigmentation and a progressive gait disorder. He had diffusely depigmented hair and skin at birth. From the age of 6 months patchy pigmentation developed, particularly in exposed regions of the skin. His hair also developed irregular pigmentation at the same time. At 6 years of age, his mother became aware that he had difficulty running and that he fell frequently. He gradually developed progressive difficulty in walking with noticeable weakness and stiffness in the legs. He was still walking at the age of 21 years but required the use of a walking aid or an assistant. He had no sensory symptoms. His intellectual and secondary sexual development was normal. He had no visual disturbance or deafness. His general health was excellent. The patient was the third child of a sibship of ten (fig 1). A 17-year-old brother and a 9-year-old sister (cases 2 and 3) had been brought to medical

attention with identical problems to those of the propositus. The patient's parents are first cousins.

The patient was intellectually normal and of average height. Scalp, eyebrow, eyelash and pubic hair were all irregularly depigmented. Patchy areas of pigmentation and "freckling" were present in the skin with other regions of hypopigmentation (figs 2 and 3). The skin texture was normal and there were no scars, telangiectasia, or skin tumours. There was no abnormal pigmentation in the buccal mucosa, palms of the hands or soles of the feet. The patient had a spastic gait with bilateral foot drop. There was no muscle wasting. The reflexes in the upper limbs were sluggish, but pathologically brisk in the lower limbs with extensor plantar responses. There was a peripheral "stocking" sensory reduction in the lower limbs to temperature, pin prick and light touch to the upper calf level. Vibration sense was absent at the ankles and knees but present at the hips. Joint position sense was normal. The peripheral nerves were not palpably enlarged. There was no scoliosis. Both cardiological and general examinations were normal.

Normal investigations included blood urea and electrolytes, full blood count, serum lipids, serum Vitamin B<sub>12</sub>, renal function tests, liver function tests, uric acid, immunoglobulin profile, syphilitic serology (negative), urinary aminoacid screen and CSF analysis. Chest, skull and spinal X-rays were all normal. A cerebral CT scan was normal and an EEG showed a mild posterior slow wave excess. Psychometry was normal.

Nerve conduction studies revealed normal motor and sensory values (median and ulnar nerves) in the upper limbs. The lateral popliteal motor conduction velocity was normal (45 m/s) although the mixed nerve action potential was small (2 uV). The sural nerve sensory action potentials were absent

Address for reprint requests: Prof WI McDonald, Institute of Neurology, The National Hospital, Queen Square, London WC1.

Accepted 10 July 1980

PEDIGREE : A.T. (1980)

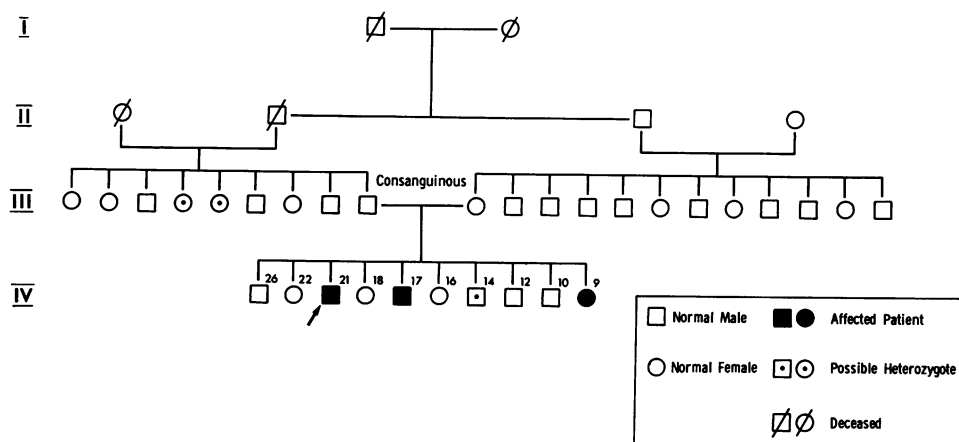


Fig 1 Pedigree of the present family.

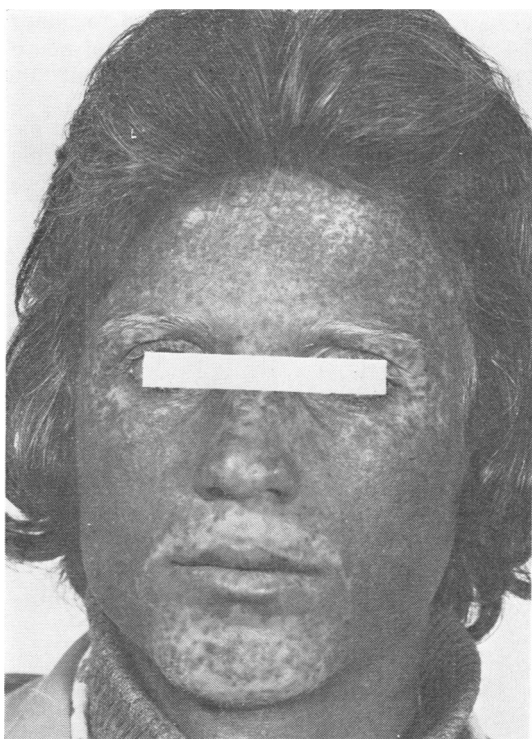


Fig 2 Case 1, showing abnormal skin and hair pigmentation. Note the contrast between dark and light hair in the eyebrows and eyelashes.

bilaterally. Sampling in tibialis anterior did not reveal any evidence of denervation. There was a grossly diminished pattern of normal units firing at

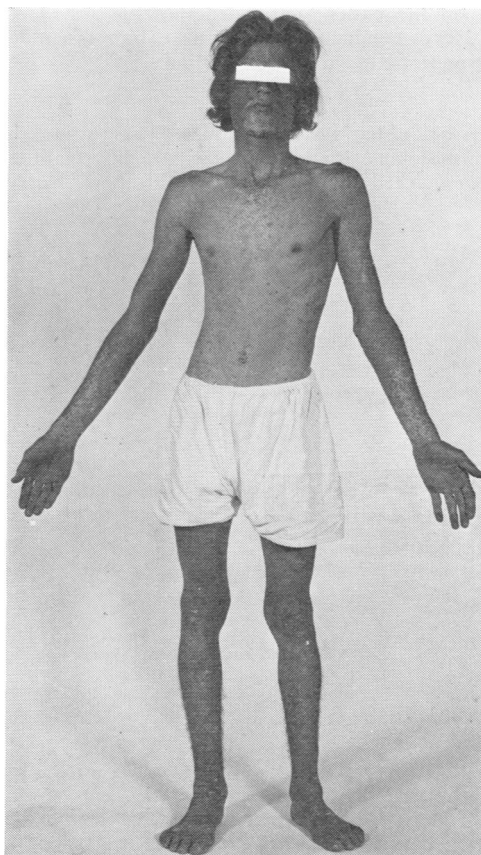


Fig 3 Case 1, showing the distribution of abnormal pigmentation.

low rates consistent with an upper motor neurone lesion. Sural nerve fascicular biopsy (Prof PK Thomas) revealed a mild depopulation of myelinated nerve fibres, with relative preservation of those of larger calibre. There was no definite evidence of regenerative activity, demyelination or hypertrophic change. The connective tissue and vasa nervorum both appeared normal. The appearances were those of an axonal neuropathy.

Skin biopsy (Dr GAK Missen) revealed a normal dermis. The epidermis was mildly acanthotic. There was striking variability in the degree of basal pigmentation, from areas of heavy pigmentation to regions of hypopigmentation (fig 4). There was no evidence of premalignancy or malignancy. DNA repair synthesis in the patient's cultured skin fibroblasts, irradiated by germicidal UV-light (254 nm), was normal (Dr FB Gianelli).

#### Case 2

The 17-year-old brother of Case 1 (fig 5) was found to have an identical disorder, with slightly less gait disability than the proband. The development of the dermatological and neurological features in the patient paralleled those of his older sibling. Nerve conduction studies also showed a mild sensory neuropathy in the lower limbs.

#### Case 3

A 9-year-old sister was also affected. As expected, both dermatological and neurological abnormalities were less marked than in her older brothers. Nerve

conduction studies again showed mild lower limb sensory neuropathy.

#### Other relatives

Two paternal aunts and a fourth sibling had abnormal facial skin "freckling" (fig 1). The remainder of the body skin and hair pigmentation was normal. They had no neurological abnormalities. Nerve conduction studies were performed on all three and were normal. This type of facial freckling is very rare in Jordan and it is likely that in the present family it is pathological and represents the heterozygous manifestation of the disease.

#### Discussion

The three patients reported here have a neurocutaneous disorder of which we have been unable to find any previous description. The expression of an identical syndrome in three siblings with unaffected consanguineous parents is consistent with an autosomal recessive mode of inheritance.<sup>2</sup> The other three relatives with dermatological abnormalities confined to abnormal facial skin pigmentation, and no neurological abnormalities probably represent the heterozygous expression of the disorder.

The dermatological hallmark is disordered pigmentation, both hypopigmentation and hyperpigmentation, of skin and hair. The neurological

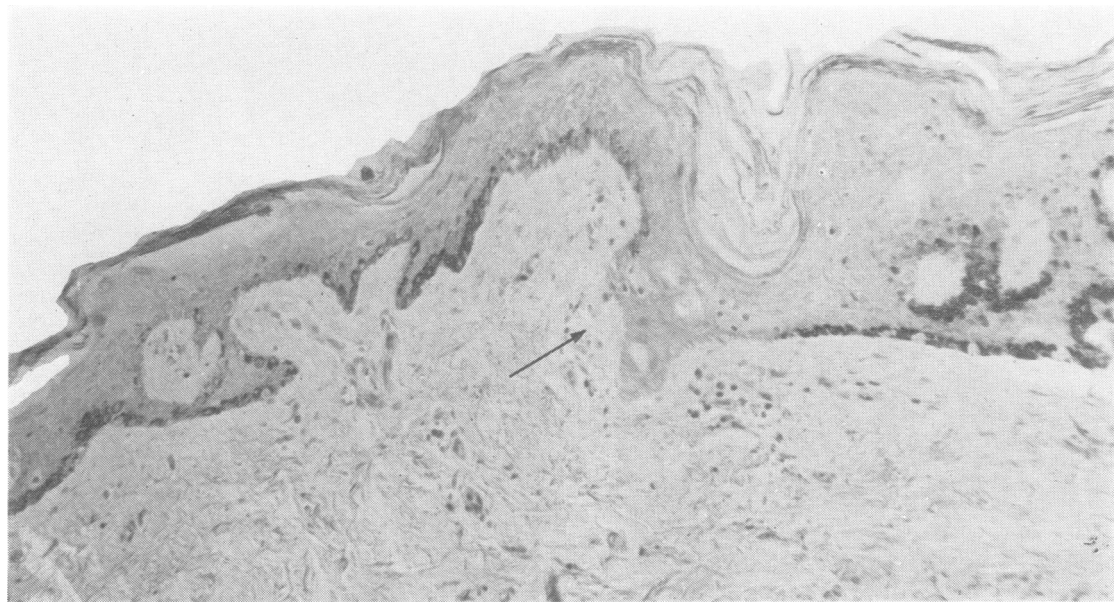


Fig 4 Section of the skin showing patchy depigmentation (arrow) in the melanocytes and cells of the stratum basale. (Masson-Fontana technique.)

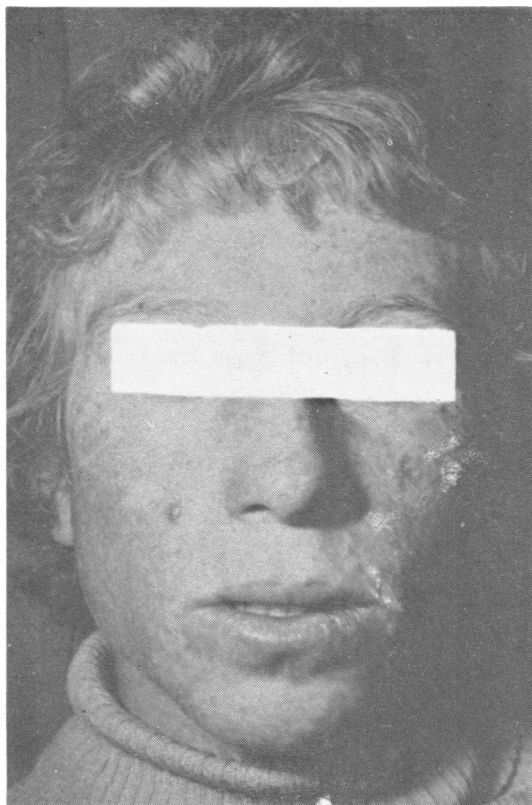


Fig 5 Case 2, showing similar cutaneous features.

picture is that of a progressive spastic paraparesis with peripheral neuropathy. A few of the large number of neurocutaneous diseases previously reported merit brief discussion in relation to our patients. Hypopigmentation occurs in a variety of neurocutaneous syndromes. Cross *et al*<sup>3</sup> described an autosomal recessive condition in three siblings in a genetic isolate. Cutaneous hypopigmentation, mental retardation and severe ocular abnormalities were present at birth, followed by spasticity and athetoid movements in infancy. Waardenberg<sup>4</sup> described an autosomal dominant condition consisting of neural deafness, facial congenital abnormalities and a white forelock. The Chediak-Higashi syndrome<sup>5</sup> is an autosomal recessive disease with partial oculocutaneous albinism, neutropenia and increased susceptibility to pyogenic infections, related to defective neutrophil function. Tissue infiltration with mononuclear cells may produce neurological abnormalities, particularly peripheral neuropathy.<sup>5</sup> The clinical picture in our patients is clearly different from that of all these

diseases.

Abnormal pigmentation also occurs in Xeroderma Pigmentosum. This is an autosomal recessive disease in which neurological abnormalities occur in 15–20% of cases.<sup>6</sup> De Sanctis and Caccione<sup>7</sup> originally described the association of Xeroderma Pigmentosum with mental deficiency, microcephaly, dwarfism and genital hypoplasia. A wide range of neurological abnormalities has subsequently been reported, including cerebellar ataxia, choreoathetosis, spasticity and peripheral neuropathy.<sup>8,9</sup> However, the dermatological features are different from those of our patients. The lack of early acute sun sensitivity and of telangiectasia, keratoses or skin tumours even in our oldest patient aged 21 years make the clinical diagnosis highly unlikely. Defective DNA repair rate of cultured skin fibroblasts after ultraviolet DNA repair in our patient (case 1) was normal. We conclude that our patients did not have Xeroderma Pigmentosum.

Spastic paraparesis also occurs in relation to a dermatosis in the autosomal recessive Sjogren-Larsson syndrome.<sup>11</sup> The clinical picture is however quite different from that of our patients, congenital ichthyosis and mental retardation being associated with spastic paraparesis.

Straightforward screening failed to reveal evidence of the metabolic abnormality in our patients. As in the case of other neurocutaneous syndromes, the mechanism of the linkage between the neurological and dermatological defects is obscure.

We are grateful to a number of colleagues who gave us expert advice: Dr M Barraitser, Dr JV Diengdoh, Dr A Gale, Dr FB Giannelli, Prof RW Gilliatt, Mr B Jay, Dr GAK Missen, Mr D Taylor, Prof PK Thomas, Dr RS Wells, and Dr RG Willison. We thank Miss Teresa Clapham for her secretarial assistance.

## References

- 1 Adams RD. Neurocutaneous diseases, Ch. 123. In: Fitzpatrick TB, ed. *Dermatology in General Medicine*, 2nd ed. New York: McGraw-Hill, 1979.
- 2 McKusick VA. *Mendelian Inheritance in Man*, 5th ed. Baltimore: Johns Hopkins University Press, 1978.
- 3 Cross HE, McKusick VA, Breen WA. A new oculocerebral syndrome with hypopigmentation. *J Pediatr* 1967; **70**:398–406.
- 4 Waardenberg PJ. A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary defects of the

- iris and head hair and with congenital deafness. *Am J Hum Genet* 1951; **3**:195-253.
- 5 Wolff SM, Dale DC, Clark RA, Root RK, Kimball HR. The Chediak-Higashi syndrome: studies of host defences. *Ann Intern Med* 1972; **76**(2):293-306.
  - 6 Aita JA. Miscellaneous neurocutaneous diseases. In: Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology*. Amsterdam: North-Holland Publishing Company, 1972; **14**:788.
  - 7 De Sanctis C, Cacchione A. L'Idioza xerodermica. *Riv speriment freniatr med legale alien ment* 1932; **56**:269-92.
  - 8 Robbins JH, Kraemer KH, Lutzner MA, Festoff BW, Coon HG. Xeroderma Pigmentosum. An inherited disease with sun sensitivity, multiple cutaneous neoplasms and abnormal DNA repair. *Ann Intern Med* 1974; **80**(2):221-48.
  - 9 Thrush DC, Holti G, Bradley WG, Campbell MJ, Walton JN. Neurological manifestations of xeroderma pigmentosum in two siblings. *J Neurol Sci* 1974; **22**:91-104.
  - 10 Pawsey SA, Magnus IA, Ramsay CA, Benson PF, Giannelli F. Clinical, genetic and DNA repair studies on a consecutive series of patients with xeroderma pigmentosum. *Q J Med* 1979; **48**(190):179-210.
  - 11 Sjogren T, Larsson T. Oligophrenia in conjunction with congenital ichthyosis and spastic disorders. A clinical and genetic study. *Acta Psychiatr Scand* 1957; Suppl 113, **1**.